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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	6

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/611,992	WU ET AL.	
	Examiner	Art Unit	
	Ruth A. Davis	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133)
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2001*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18)☐ Interview Summary (PTO-413) Paper No(s). _____
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other

DETAILED ACTION

Applicant's amendments filed April 9, 2001 have been received and entered. Applicant's arguments have been fully considered.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1 – 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 13, 27 and their dependents are drawn to a method for cultivation of filamentous fungi however are rendered vague and indefinite for reciting "suitable for mycelia attachment" because the phrase does delineate what is considered "suitable" for mycelia attachment.

Claims 7, 15, 23 and their dependents are drawn to a method for cultivation of filamentous fungi however are rendered vague and indefinite because it is not clear if step b additionally comprises culturing said fungi/species prior to introduction into said medium or if step b is replaced with culturing fungi prior to introduction into said medium.

Claim 24 recites the limitation "the filamentous fungi" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

3. Claims 1 – 4, 6 – 13, 15 – 21 and 23 – 28 originally rejected under 35 U.S.C. 102(e) as being anticipated by Wu et al. (May 2000) have been withdrawn upon receipt of certified translation of priority document, Taiwanese Patent Application Serial No. 89103793.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1 – 4, 13 and 21 stand rejected under 35 U.S.C. 102(b) as being anticipated by Yamaguchi et al. (US 3,765,906).

Applicant argues Yamaguchi et al. does not describe a method for cultivating filamentous fungi in a bioreactor using a nutritionally solid substrate suitable for mycelia attachment. However, this argument is not found persuasive because the methods of Yamaguchi et al. teach a culture medium containing rice powder in which a Monascus species is innocluated. It is inherent in the methods of Yamaguchi et al. that the rice powder substrate was suitable for mycelia attachment because it is a nutritionally solid grain substrate. Moreover, by practicing the methods of Yamaguchi et al., it is inherent that one would be practicing the methods as claimed by applicant.

Applicant claims a method for cultivation of filamentous fungi and metabolites thereof, whereby said fungi may be Monascus, Penicillium, or Aspergillus, comprising the steps of: preparing a medium with a nutritionally solid substrate, specifically grain, inoculating the fungi into the medium and placing it in a bioreactor for fermentation.

Yamaguchi et al. teaches a method for cultivating a Monascus species and non-soluble pigments thereof, whereby a culture medium containing rice powder is inoculated with a Monascus species and is placed in a jar fermentor for fermentation (col.3 example 1).

The reference anticipates the claimed subject matter because the culture medium contains a nutritionally solid substrate (e.g. rice powder) in which a filamentous fungi, Monascus, is inoculated. It is inherent in the methods of Yamaguchi et al. that the rice powder substrate was suitable for mycelia attachment because it is a nutritionally solid grain substrate. Moreover, by practicing the methods of Yamaguchi et al., it is inherent that one would be practicing the methods as claimed by applicant.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 6, 11 – 12, 19 – 20 and 27 – 28 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi et al. (US 3,765,906) in view of Johal et al. (US 4,954,440) and Eyal et al. (US 5,077,201).

Applicant argues that Yamaguchi et al., Johal et al. and Eyal et al. do not teach a substrate suitable for mycelia attachment. However, this argument is not found persuasive because Yamaguchi et al. teach a nutritionally solid substrate, (e.g. rice powder), that is provided in a culture medium in which a Monascus species is inoculated (example 3). Johal et al. provides motivation for adding a nitrogen source, inorganic nutrients, trace salts and elements (col.4 line 29-24, 48-53) as well as the use of batch fermentation and the fed batch process (col.3 line 35-30) for the reasons stated in the prior office action. Eyal et al. further supports the motivation to one of ordinary skill in the art to employ the fed batch process, also stated in the prior office action.

Applicant claims a method for cultivation of filamentous fungi and metabolites thereof, whereby said fungi may be Monascus, Penicillium, or Aspergillus, comprising the steps of preparing a medium with a nutritionally solid substrate, nitrogen source, inorganic salts and trace

elements, inoculating said fungi into the medium and placing it in a bioreactor for fermentation using the fed batch process, wherein the batch medium comprises a nitrogen source and nutritionally solid substrate.

Yamaguchi et al. teaches a method for cultivating a Monascus species and metabolites thereof, wherein a culture medium containing rice powder is inoculated with a Monascus species and is placed in a jar fermentor for fermentation (col.3 example 1). The reference teaches a culture medium containing a nutritionally solid substrate (e.g. rice powder) in which a filamentous fungi, Monascus, is inoculated.

The reference does not teach a medium additionally comprising a nitrogen source, inorganic salts and trace elements or cultivating the fungi with the fed batch process wherein the batch medium contains a nitrogen source and a nutritionally solid substrate. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include a nitrogen source, inorganic salts and trace elements in the culture medium of Yamaguchi because Johal et al teaches a nutrient medium for the cultivation of filamentous fungi normally contains nitrogen sources, inorganic nutrients such as trace salts and trace elements (col. 4 lines 29-24, lines 48-53). In addition, Johal et al teaches typical cultivation methods employed for filamentous fungi in include batch fermentation and the fed batch process (col.3 lines 25-30). One would have been motivated by Johal et al at the time the invention was made to include the additional nutrients, as they are part of the minimal medium requirements to sustain growth and production of successful filamentous fungi.

One of ordinary skill in the art would have been further motivated to utilize the fed batch process in the method of Yamaguchi et al because Eyal et al discloses that the fed batch process

is advantageous to maximize production of fungal metabolites (col. 4 lines 15-18). Furthermore, the inclusion of a nitrogen source and nutritionally solid substrate to the batch medium would have been obvious to one of ordinary skill in the art because with additional media supplied via fed batch, the fungi would need an adequate replenishment of nutrients as it utilized its original source.

9. Claims 5, 7 – 8, 14 – 16 and 22 – 24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi et al. (US 3,765,906) in view of Yueh et al. (PN 4,418,080) and Haas et al. (PN 4,031,250).

Applicant argues that Yamaguchi et al., Yueh et al. and Haas et al. do not teach a substrate suitable for mycelia attachment. However, this argument is not found persuasive because Yamaguchi et al. teach a nutritionally solid substrate, (e.g. rice powder), that is provided in a culture medium in which a Monascus species is inoculated (example 3). Furthermore, it is reiterated that Yueh et al. teach a method wherein a Monascus species is fermented on a nutritionally solid substrate such as wheat or barley (col.1 line 38-42). Yueh et al. and Hass et al. provide motivation for known processes commonly used in the art at the time of the invention as discussed in the prior office action.

Applicant claims a method for cultivation of filamentous fungi and metabolites thereof, specifically Monascus, whereby a medium is prepared comprising a nutritionally solid substrate, specifically grain, and is inoculated with an inoculum of said fungi then placed in a bioreactor for fermentation. The grain is previously husked, cocked, and sterilized. The inoculum is

obtained from a stock fungi that is cultured on an agar plate, incubated, washed, and cultivated in a medium containing said substrate via shaking.

Yamaguchi et al teaches a method for cultivating a Monascus species and metabolites thereof, wherein a culture medium containing rice powder is inoculated with a Monascus species and is placed in a jar fermentor for fermentation (col.3 example 1). The reference teaches a culture medium containing a nutritionally solid substrate (e.g. rice powder) in which a filamentous fungi, Monascus, is inoculated.

The reference does not teach using a stock culture as the source of said fungal inoculum whereby the stock culture is grown on an agar plate, washed, cultivated in suspension with a grain substrate in an incubator while shaking, and placed in a bioreactor for fermentation. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to obtain the fungal inoculum from a stock culture as claimed by applicant because Yueh et al. teaches the cultivation of Monascus in a medium containing a solid grain substrate, specifically wheat or barley, (abstract; col.1 lines 38-40, 43-45; col.2 lines 38-42) whereby an inoculum of Monascus is prepared from a previously grown liquid culture which is incubated while shaking (example II). The grain is pre-sterilized by moist heat or autoclave (col.2 lines 19-22). The previously grown culture is disclosed as obtainable by any known method in the art (col.2 lines 13-16). The obtained inoculum is further inoculated into the nutritionally solid substrate medium and allowed to ferment (col.2 lines 27-31).

Yueh et al. does not disclose the specific use of an agar plate to grow the stock culture, however, Haas et al. teaches the cultivation of Monascus on a grain substrate whereby the culture is obtained from a stock culture grown on an agar slant or potato dextrose agar (col.1 lines 56-

63). The reference further teaches that a fungal suspension in liquid medium is typically formed prior to being inoculated into a grain substrate (col.2 lines 5-8). For example, the slant or agar plate on which the fungus was grown is washed with water to ensure a turbid suspension (col.2 lines 8-12). The suspension is then inoculated into a grain-containing medium (col.2 lines 12-13) where in the grain is heated/autoclaved for sterilization (col.1 lines 65-68). The resulting culture is further utilized to inoculate media for fermentation (col.2 lines15-16).

One of ordinary skill in the art would have been motivated at the time the invention was made to prepare an inoculum as disclosed by the above references for use in the method of Yamaguchi et al because they are commonplace and typical procedures that are practiced by those skilled in the art. Further, it would have been obvious to one of ordinary skill to husk and cock the grain prior to sterilization because they are conventional steps in preparing grain to necessitate its use.

10. Claims 9-10, 17-18 and 25-26 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi et al. (US 3,765,906) in view of Yueh et al. (PN 4,418,080) and Haas et al. (PN 4,031,250), and in further view of Tung et al. (Bioprocess Eng, 1997, 17 (1) p.1-5).

Applicant argues that Yamaguchi et al., Yueh et al., Haas et al. and Tung et al. do not teach a substrate suitable for mycelia attachment used in a bioreactor. However, this argument is not found persuasive because Yamaguchi et al., Yueh et al. and Hass et al. each use a nutritionally solid grain substrate (e.g. rice powder in Yamaguchi et al., wheat or barley in Yueh et al., and corn or rice in Hass et al. (abstract)) as discussed above and in the prior office action.

Tung et al. provides motivation for using a bioreactor, specifically a pneumatic airlift bioreactor with a net draft tube, wherein at the time of the invention, it was known to be advantageous for its shortened cultivation time during fermentation (established and cited in the prior office action).

Applicant claims a method for cultivation of filamentous fungi and metabolites thereof, specifically Monascus, whereby a medium is prepared comprising a nutritionally solid substrate, specifically grain, and inoculated with an inoculum of said fungi then placed in a pneumatic airlift bioreactor with a net draft tube for fermentation. Prior to addition to the medium, the grain is husked, cocked, and sterilized. The inoculum is obtained from a stock fungi that is cultured on an agar plate, incubated, washed, and cultivated in a medium containing said substrate via shaking.

Yamaguchi et al. teaches a method for cultivating a Monascus species and metabolites thereof, wherein a culture medium containing rice powder is inoculated with a Monascus species and is placed in a jar fermentor for fermentation (col.3 example 1). The reference teaches a culture medium containing a nutritionally solid substrate (e.g. rice powder) in which a filamentous fungi, Monascus, is inoculated.

The reference does not teach using a stock culture as the source of said fungal inoculum whereby the stock culture is grown on an agar plate, washed, cultivated in suspension with a grain substrate in an incubator while shaking, and placed in a bioreactor for fermentation. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to obtain the fungal inoculum from a stock culture as claimed by applicant because

Yueh et al. teaches the cultivation of Monascus in a medium containing a solid grain substrate (abstract; col.1 lines 38-40, 43-45; col.2 lines 38-42) whereby an inoculum of Monascus is prepared from a previously grown liquid culture which is incubated while shaking (example II). The grain is pre-sterilized by moist heat or autoclave (col.2 lines 19-22). The previously grown culture is disclosed as obtainable by any known method in the art (col.2 lines 13-16). The obtained inoculum is further inoculated into the nutritionally solid substrate medium and allowed to ferment (col.2 lines 27-31).

Yueh et al. does not disclose the specific use of an agar plate to grow the stock culture, however, Haas et al. teaches the cultivation of Monascus on a grain substrate whereby the culture is obtained from a stock culture grown on an agar slant or potato dextrose agar (col.1 lines 56-63). The reference further teaches that a fungal suspension in liquid medium is typically formed prior to being inoculated into a grain substrate (col.2 lines 5-8). For example, the slant or agar plate on which the fungus was grown is washed with water to ensure a turbid suspension (col.2 lines 8-12). The suspension is then inoculated into a grain-containing medium (col.2 lines 12-13) where in the grain is heated/autoclaved for sterilization (col.1 lines 65-68). The resulting culture is further utilized to inoculate media for fermentation (col.2 lines15-16).

One of ordinary skill in the art would have been motivated at the time the invention was made to prepare an inoculum as disclosed by the above references for use in the method of Yamaguchi et al because they are commonplace and typical procedures that are practiced by those skilled in the art. Further, it would have been obvious to one of ordinary skill to husk and cock the grain prior to sterilization because they are conventional steps in preparing grain to necessitate its use.

The above references do not teach the use of a pneumatic airlift bioreactor with a net draft tube, however it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize this type of bioreactor because Tung et al. teaches an airlift reactor with double net draft tubes is advantageous for fermentation in that cultivation time is significantly shortened (abstract). Tung et al. further teaches single net draft tubes perform better than a bubble column (introduction). One of ordinary skill in the art would have been motivated to utilize the single or double net draft tube over a bubble column in the methods of the references cited above to improve the efficacy of the fermentation process and to increase production and scale up efficiency.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruth A. Davis whose telephone number is 703-308-6310. The examiner can normally be reached on M-H (7:00-4:30); altn. F (7:00-3:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

June 15, 2001

LEON B. LANKFORD, JR.
PRIMARY EXAMINER